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THE COUNCIL FOR TOBACCO RESEARCH–U.S.A., INC.

110 EAST 59TH STREET
NEW YORK, N. Y. 10022
(212) 421-8885

JUL 29 1974

Application for Research Grant
(Use extra pages as needed)

Date 7.16.74

1. Principal Investigator (give title and degrees):

Edward Leete, Professor of Chemistry, B.Sc., Ph.D., D.Sc.

2. Institution & address:

University of Minnesota
Minneapolis
Minnesota, 55455.

3. Department(s) where research will be done or collaboration provided:

Department of Chemistry

4. Short title of study:

Synthesis and Biological Activity of Nicotine Analogs

5. Proposed starting date: 1.1.75 (This is a continuation of CTR grant No. 929)

6. Estimated time to complete: 2 years

7. Brief description of specific research aims:

Analogs of nicotine will be prepared for pharmacological testing. The biological tests will be carried out by Professor Von Euler, Karolinska Institute, Stockholm, and by Dr. Åke Pilotti of the Swedish Tobacco Company.

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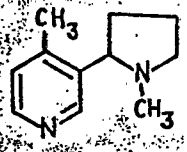
Source: https://www.industrydocuments.ucsf.edu/docs/mxdm0000

8. Brief statement of working hypothesis:

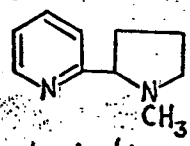
Our general plan is to prepare nicotine analogs for biological testing (see section 9. for the biological tests to be carried out) in the hope that we will learn something about the structural features required for "Nicotinic Activity" . Since there is considerable commercial interest in "synthetic tobacco" it is possible that some of these derivatives of nicotine which will be prepared will be more desirable components of the tobacco than nicotine itself. For example they could plausibly be added to a "synthetic tobacco" yielding a product with good smoking qualities but without some of the deleterious effects of nicotine.

9. Details of experimental design and procedures (append extra pages as necessary)

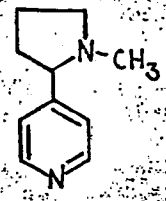
In our first progress report (covering the period 1.1.74 to 6.30.74) details of the synthesis of the following nicotine analogs are outlined . These compounds are being resolved into their optically active enantiomorphs and samples will be submitted to Dr. Von Euler



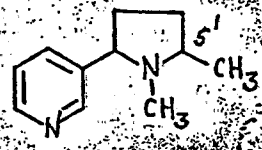
4-methylnicotine



α-nicotine



γ-nicotine

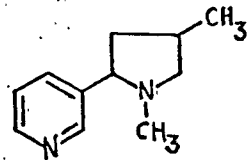


cis-5'-methylnicotine

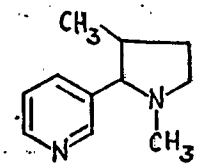
for the following tests :

1. Isolated rabbits jejunum
2. The guinea-pig ileum
3. The blood pressure of the cat
4. The isolated rectus abdominus muscle of the frog Rana temporaria

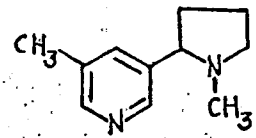
Dr. Åke Pilotti will test these and other analogs in a human cancer tissue culture which he has developed. Other analogs of nicotine which are to be made are illustrated below.



4'-methylnicotine



3'-methylnicotine



5-methylnicotine

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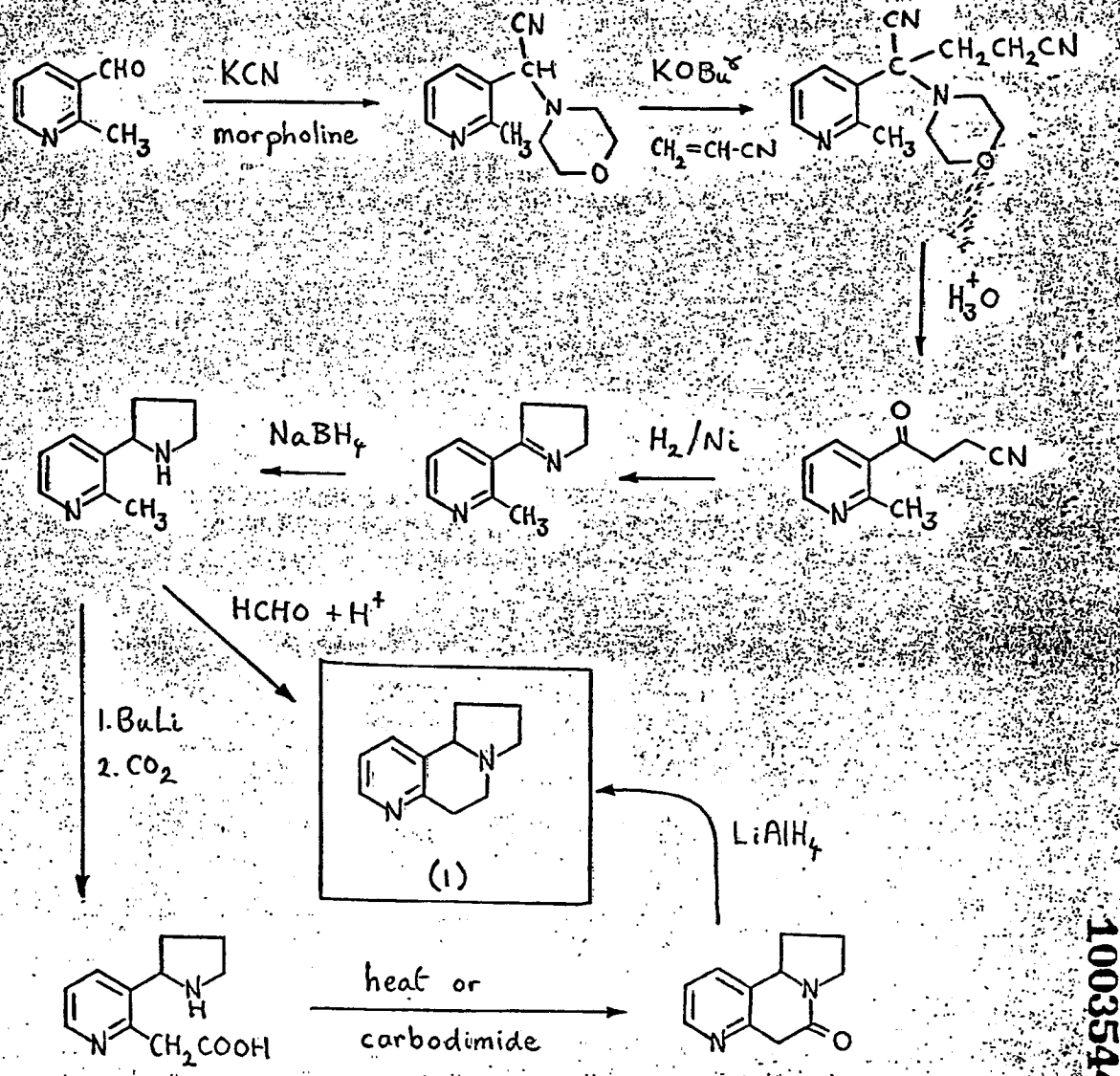
Source: https://www.industrydocuments.ucsf.edu/docs/mxdm0000

The synthesis of these compounds will follow the general synthesis outlined in our original research proposal (Grant No. 929) . A compound of considerable interest is the tricyclic analog (1) . In this molecule the pyrrolidine ring will have a fixed conformation relative to the pyridine ring . The biological properties of this compound will be of great interest since it has been suggested that free rotation of the pyrrolidine ring relative to the pyridine ring is required for "Nicotinic Activity" . We plan to make this compound by the following route which we think has a reasonable chance of success. Previous attempts to make this compound have failed (F. Haglin, Acta Pharm. Suecica 4, 117 (1967)).



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Source: https://www.industrydocuments.ucsf.edu/docs/mxdm0000

10. Space and facilities available (when elsewhere than item 2 indicates, state location):

The chemistry department at the University of Minnesota has well equipped laboratories for chemical research. Most of my research group (currently 11 graduate students and one postdoctoral fellow) are housed in a new building (Kolthoff Hall) which was occupied in April 1970. I have a private research laboratory in which I take especial pride in working with my own hands for 30 to 40 hrs per week . My graduate students are in 4-man modules. The instruments available to my group are the following: Chromatronix Series 3500 high pressure liquid chromatograph, 2 Gilson fraction collectors, an LKB fraction collector, a Varian XL-100 nmr spectrometer (with Fourier transform C-13), and AEI-MS-30 high and low resolution mass spectrometer, a Cary 11 uv spectrophotometer, a Perkin Elmer ir spectrophotometer,a Cary 60 ord spectrophotometer, a Nuclear Chicago Mark II liquid scintillation counter. A greenhouse is available on the roof of the chemistry building where tobacco and other plants are grown. Rooms are also available for the extraction of plants, for hydrogenations, and for the culture of micro-organisms.

11. Additional facilities required:

None

12. Biographical sketches of investigator(s) and other professional personnel (append):

Edward Leete (principal investigator) Philip Hoekstra (graduate student)
Tony Catka (graduate student)

13. Publications: (five most recent and pertinent of investigator(s); append list, and provide reprints if available):

list appended

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R: REDACTED MATERIAL

Item 12 (continued)

Biographical sketches of the professional personnel

Edward Leete (Principal Investigator)

REDACTED

REDACTED

REDACTED

Philip Hoekstra (3 rd. year graduate student)

REDACTED

REDACTED

Tony Catka (1 st. year graduate student)

REDACTED

REDACTED

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Source: https://www.industrydocuments.ucsf.edu/docs/mxdm0000

Item 13

Recent Publications (reprints are attached at the end of this application)

1. E. Leete and Yu-Ying Liu , Metabolism of [2-^{3}H]- and [6-^{3}H]-nicotinic acid in intact Nicotiana tabacum plants. Phytochemistry, 12,593 (1973).

2. E. Leete, Biosynthesis and Metabolism of the Tobacco Alkaloids, Proceedings of the First Philip Morris Science Symposium, Nicholas J. Fina, editor, 1973, p.92.

3. E. Leete and G. B. Bodem, Biosynthesis of Shihunine, an Alkaloid of the Orchid Dendrobium pierardii, J. C. S. Chem. Commun., 522 (1973).

4. E. Leete, Biosynthesis of Alkaloids, Chapt. 4 in Biosynthesis 2 , ed. T. A. Geissman, A Specialist Periodical Report of the Chemical Society, London, 1973, p.106.

5. E. Leete, G. E. Davis, C. R. Hutchinson, K. W. Woo, and M. R. Chedekel, Biosynthesis of Azetidine-2-carboxylic Acid in Convallaria majalis, Phytochemistry, 13, 427 (1974).

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Source: https://www.industrydocuments.ucsf.edu/docs/mxdm0000

R: REDACTED MATERIAL

14. First year budget:

A. Salaries (give names or state "to be recruited") Professional (give % time of investigator(s) even if no salary requested)	% time	Amount
Edward Leete (one month summer salary)		REDACTED
Philip Hoekstra (research assistant)		
Tony Catka (research assistant)		
Fringe benefits on the above salaries (calculated at 17.5%)		
Technical:		
Sub-Total for A		R
B. Consumable supplies (by major categories)		
Chemicals (organic compounds, solvents etc.)		3500
Glassware		1500
Sub-Total for B		5000
C. Other expenses (itemize):		
Analytical services (mass spectra, nmr, CHN)		600
Page charges for journal articles		300
Travel to one domestic scientific meeting		300
Sub-Total for C		1200
Running Total of A + B + C		21005
D. Permanent equipment (itemize):		
none		
Sub-Total for D		0
E. Indirect costs (15% of A+B+C)		3150
Total request		24155

15. Estimated future requirements:

	Salaries	Consumable Suppl.	Other Expenses	Permanent Equip.	Indirect Costs	Total
Year 2	16000	5000	1200	0	3300	25530
Year 3						

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Source: https://www.industrydocuments.ucsf.edu/docs/mxdm0000

16. Other sources of financial support:
List financial support from all sources, including own institution, for this and related research projects.

CURRENTLY ACTIVE

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates
Synthesis and Biological activity of nicotine analogs	Council for Tobacco Research No. 929	$23709	01/01/74 to 12/31/74
Metabolism of Natural Products of Medicinal Interest	NIH-GM-13246-17 (the terminal year of a 5 year grant period	$ 46810	01/01/74 to 12/31/74

PENDING OR PLANNED

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates
Metabolism of Natural Products of Medicinal Interest	NIH-GM-13246-18 (Funds are tight in this branch of the NIH and it is dubious that this full amount will be granted)	$ 63615	01/01/75 to 12/31/75

It is understood that the investigator and institutional officers in applying for a grant have read and accept the Council's "Statement of Policy Containing Conditions and Terms Under Which Project Grants Are Made."

Principal investigator

Typed Name Edward Leete

Signature Edward Leete Date 7.16.74

Telephone 612 (Area Code) 373 (Number) 2380 (Extension)

Checks payable to

University of Minnesota

Mailing address for checks

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University of Minnesota

Minneapolis, MN, 55455.

Responsible officer of institution

Typed Name Clinton T. Johnson

Title Asst. Vice President, Business Administration

Signature X C. T. Johnson Date

Telephone 612 (Area Code) 376 (Number) 7614 (Extension)

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Source: https://www.industrydocuments.ucsf.edu/docs/mxdm0000